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SUBSEQUENT CLINICAL OBSERVATIONS

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SUBACUTE-CHRONIC "ARSENIC" POISONING IN INFANTS -- SUBSEQUENT CLINICAL OBSERVATIONS
[Nyūji ni mirareta akyūsei naishi mansei "hiso" chūdoku -- Sono go no rinshō kansatsu]

By

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I. Introduction

Exactly 4 months have gone by since we reported on "Two months of clinical observations of subacute-chronic arsenic poisoning in infants" [1]. In other words, a period of a half year has passed by since it became known that the present incident was caused by arsenic poisoning from "MF powdered milk." This report deals with the subsequent progress of the patients, the results of tests which were still incomplete at the time of the previous report, and other matters. In particular, there are some types of findings concerning which it is necessary for a certain period of time to elapse before it is possible to determine whether arsenic poisoning is the cause or not. In this sense, it is believed of importance to sum up the observations after a period of 6 months has elapsed.

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(30)

II. Subsequent Progress and Clinical Findings

1. General State of Patients. Let us repeat the state as of November 24 of last year, as given in the appendix to the previous report. The number of patients suffering from infantile arsenic poisoning was 134 cases. Of these, six cases were currently hospitalized, and 119 were being given outpatient treatment (in 113 of these cases, abnormal findings were not observed, and in six cases there were abnormal findings of one type or another which were regarded as being caused by arsenic). There were eight cases who did not come to the hospital, and there was one death due to causes other than arsenic poisoning. That is, among the 134 cases there was a total of 12 cases displaying abnormal findings. To classify them by causes (including both the hospitalized cases and the outpatient cases), there were 10 cases with liver changes, one case with blood picture changes (neutrocytopenia), and one case with abnormalities in the nails. In the following, we describe their subsequent progress.

All of the six hospitalized patients had improved and were discharged by the end of December of last year. However, there were two cases which did not conform to our standards for determining improvement and discharge, as described in the previous report. Both of these cases still had some abnormal findings in their liver functions (although they conformed with the Ministry of Health and Welfare's standards for determining cure of infants suffering from this condition [25]). However, their discharge was permitted in consideration of family conditions. Among the six outpatient cases, those who had displayed abnormalities in their liver function tests have returned to a more or less normal condition, as is described below. In view of these circumstances, from around the middle of last December the patients have been coming to the hospital for monthly visits so that their progress can be observed. No doubt because of improvement, as described above, the number of outpatient cases has declined to 59 this year. The others are not visting the hospital.

2. Concerning Melanosis. In each separate case of arsenic poisoning, the period of time required for disappearance of arsenmelanosis differs widely. Just as it is difficult to establish the period of appearance of arsenmelanosis, so also the time boundaries when melanosis disappears and returns to normal are unclear. Thus, there is great uncertainty about this point, and the literature contains no definite information [2]. We made an attempt to establish this. Since our survey is based mainly on outpatients who visit the hospital irregularly, the information is necessarily somewhat general. However, the times when the melanosis disappeared were as follows. Among the 53 cases for which there were clear records, it disappeared within 1 month in three cases (5%), after 1 to 2 months in 28 cases (53%), after 2 to 3 months in 19 cases (36%), and after 3 to 4 months in three cases (5%). Thus, in the vast majority of cases (95%), the melanosis became unnoticeable within a period of 1 to 4 months. This arsenmelanosis disappeared within 4 months in all the cases.

3. White Spots and Desquamation. Just as in the case of melanosis, it is unclear how long is required for these to disappear completely. Since we are dealing here chiefly with outpatients, there are some points which it is difficult to establish with accuracy. However, the results may be summed up in general as follows. Of the 68 cases whose records contain definite statements that these symptoms disappeared, they disappeared within 1 month in five cases (7%), after 1 to 2 months in 38 cases (56%), after 2 to 3 months in 20 cases (29%), after 3 to 4 months in four cases (6%), and after 6 to 7 months in one case (1%). Just as in the case of the melanosis, in 93% of the cases the white spots and desquamation disappeared within a period of 3 months.

4. Abnormalities in the Nails. As one would naturally assume, the abnormalities in the nails, described in the previous report, would also tend to disappear within the passage of time. The data were summarized for the 61 outpatient cases in which clear information was available. That is, they

disappeared within 1 month in four cases (8%), after 1 to 2 months in 19 cases (37%), after 2 to 3 months in 22 cases (42%), and after 3 to 4 months in six cases (12%). They were still present in one case (2%). This case with abnormalities still present is the one whose nails were photographed in color, and the color photographs were given in the previous report [1]. In the findings at the beginning of March, normal nails had begun to appear at about 1 mm at the base of the nails. From the above, it was learned that the abnormalities in the nails recovered in 87% of the cases within a period of up to 3 months. It is clear from the preceding that the three symptoms above (melanosis, white spots and desquamation, and abnormalities in the nails) return to normal at approximately the same time, although there are some differences from case to case. Abnormalities in the nails would appear to be the slowest to recover.

5. Hyperkeratosis. In addition to the two cases mentioned in the previous report [1], this was observed subsequently in only one additional case. It was observed in the fourth month in this case, chiefly in the thumbs. All cases had returned to normal within a period of 4 to 5 months. A noteworthy finding in the current cases of infantile arsenic poisoning is the fact that there are very few cases of hyperkeratosis. The reasons for this were mentioned in the previous report.

6. Other Changes. The cases which had thinning-out of their hair on the head or of the eyebrows gradually returned to their premorbid state. During this year, those in charge of their upbringing state that they have more or less returned to their premorbid state.

Among changes in the mucous membranes, cases with pigmentation of the mucous membranes of the gums have undergone no subsequent changes. Therefore, it would seem to be difficult to recognize this as being caused by arsenic.

There were three cases displaying slight blackish ridges on the incisors at a short distance away from the gums. These symptoms have not undergone

any changes subsequently, and it is therefore doubtful whether they are caused by arsenic.

In about one-fifth of the cases, there was palpation of the spleen, as mentioned in the previous report [1]. Palpation continued in most of these cases subsequently, with little change. Therefore, connection with arsenic is doubtful.

7. State of Growth of Patients. In order to determine what effects resulted from the arsenic, we made a study of the body weights of the patients, which are the most vivid indicators of the state of growth of infants. In the previous report we gave the results of a comparison of the body weights of the patients with the standard body weight table published by the Ministry of Health and Welfare [3]. Seventy-four percent of the cases were within the normal range, while 14% were above and 12% were below normal. This time, we studied the body weight distribution between last November and the beginning of March of this year, that is, within the period of 3 to 6 months afterwards. Of the 79 cases, 66% of the total were within the normal range, while 23% were above and 11% were below normal. It is noteworthy that some patients had remarkably improved nutrition, while generally speaking there was improvement in the state of nutrition. The state of weight increase was good, as is shown in Table 1, where is shown the average monthly weight increase ratio, viewed on the basis of the differences in the measured values of the body weight between the time of the first examination and the time of the last examination.

III. Clinical Tests

Here let us describe the test items in which abnormalities were still seen at the time of the previous report [1] or concerning which it was not possible to give a detailed account.

Tab. 1 Average Weight Increase per Month

Average weight increase per month / Age (Mo.) at the last examinaion	100gm>		101~200		201~300		301≦		Total	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
1~3 M.	0	0	0	0	0	0	0	0	0	0
4~7 M.	0	0	0	1	0	0	7	4	7	5
8~12M.	0	0	4	0	9	5	6	5	19	10
13~24M.	2	0	2	3	6	5	7	6	17	13
25M≦	0	0	2	0	0	0	0	1	2	1
Total	2	0	8	4	15	10	20	15	45	29

1. Electrocardiograms

We studied 105 cases of infantile arsenic poisoning for their PQ interval, QT interval, T waves and ST. The results were described in outline in the previous report. Here let us given more detailed description of the results of the study. The standard arm leads were used in the tests. The periods of the first tests extended from September 6 to October 19. Those with abnormalities were studied until they subsequently returned to normal.

1) Concerning the PQ interval. Prolongation of the PQ interval signifies prolongation of the atrioventricular conduction interval. In adults, a value of more than 0.20" is considered to be prolonged, but in infants this PQ interval varies with the age and with the RR interval. Ohr and Porscha [4] state that the maximum limit in infants is 0.12-0.14". Ziegler [5] indicates the values of 0.12" for 3-6 months and 0.14" for 6-12 months. Hamada [6] made a mathematical-statistical study of the relationship between the PQ and RR. He calculated a formula of PQ = 0.77RR + 7.58 (unit 1/100 sec) and stated that the critical limit is ±3.0 with a level of significance of 1% or less.

We obtained the results shown in Fig. 1 for the PQ-RR relationship in patients with infantile arsenic poisoning. The horizontal line in the center

is Hamada's mean value, and the lines above and below it are the ±3.0 limits. The percentage below the mean was 51.5%; the percentage above the mean was 42.8%; and there was prolongation in 5.7% of the cases. The progress of the six cases displaying prolongation, as well as of one borderline case, was observed, and the changes shown in Fig. 2 were obtained after 2 months. In five cases, there was a return to within the normal range within 2 months. In one case, there was still prolongation after 2 months, but there was return to within the normal range after 3 months. In one case, there was still prolongation after 1 month, but a return to within the normal range after 2 months. That is, all cases returned to normal values within 3 months.

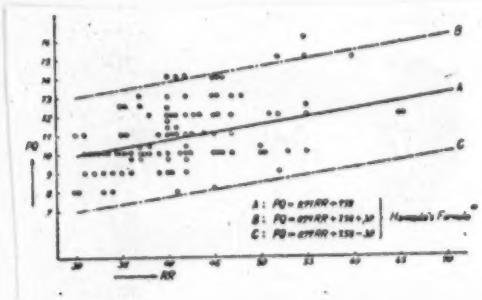

Fig. 1. Relation between PQ interval and RR interval in the patients at the first examination.

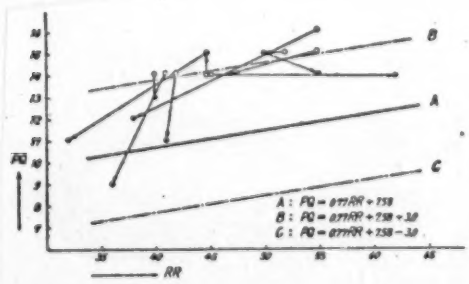

Fig. 2. Successive changes in PQ interval of the patients who showed PQ prolongation at the first examination.

2) Concerning the QT interval. The QT interval corresponds to the electrical excitation period of the ventricle. The start of Q precedes ventricular systole, and the end of T coincides more or less with the conclusion of systole, although there are times when it is somewhat earlier or later. QT prolongation [7] is frequently observed in myocardosis and appears also in hypocalcemia, but in this case there will be a prolongation of the ST horizontal section. Ziegler is of the opinion that the maximum limit is 0.30" for infants of 3 to 12 months. Hamada [8] recognizes that there is a correlation between the QT and the RR. He derives a formula of QT = 1/4 RR + 14.1 (unit 1/100 sec) and states that the critical limit is ±3.3 with a level of significance of 1% or less.

For the relationship between QT and RR, we obtained the results shown in Fig. 3 for the above 105 cases. The horizontal line in the middle is Hamada's mean value, and the lines above and below it are the ±3.3 limits. The percentage below the mean was 45.7%; the percentage above the mean was 48.6%; and there was prolongation in 5.7% of the cases. Five cases with prolongation and the one borderline case all returned to the normal range within 2 months, and one case returned to the normal range after 3 months. Among those displaying a decline in T, there was one case which was in the normal range at the beginning, but displayed prolongation after 20 days, then went into the normal range after 2 months (Fig. 4). In all cases of QT prolongation, there was no conspicuous prolongation of the ST horizontal section.

3) Concerning T waves. Decline or flattening of the T waves signifies myocardosis. However, changes do not necessarily occur only during myocardosis, and changes sometimes are caused also by dysfunctions. According to Seham [9], the T waves of infants abound in changes, there being great high-low differences; and it would be easy to fall into error if a value of less than 2 mm in the T waves in the I and II leads were taken as a T decline, as is done in the case of adults. In our cases as well, we found that if adult standards are followed

for establishing T decline, there would be a larger number of cases, most of which would be concentrated to an extreme degree in cases with a short RR interval. Umeno [10, 11] argues that cases with values of less than 1 mm in all three leads ought to be treated as T decline. According to this standard, T decline was observed in two of the above 105 cases. One of these cases also had QT prolongation, and the other case had PQ prolongation. Both cases returned to normal within 1 month. Their subsequent progress was followed up, but they are normal.

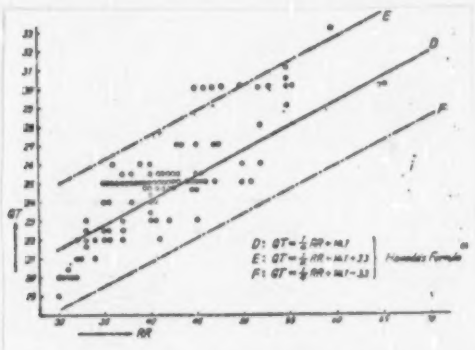

Fig. 3. Relation between QT interval and RR interval in the patients at the first examination.

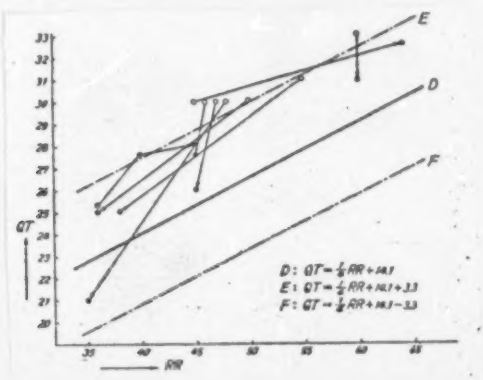

Fig. 4. Successive changes in QT interval of the patients who showed QT prolongation at the first examination.

4) Concerning ST. No cases of ST decline could be observed. There was only one case with prolongation of both PQ and QT.

From the preceding, we may state concerning the 105 cases of infantile arsenic poisoning examined by us that studies of the PQ interval, QT interval, T waves and ST revealed that prolongation of PQ and QT was observed in 6.6% and 6.6%, respectively, that most of these had returned to the normal range after 2 months, that T decline was observed in 1.9% with subsequent return to normal within 1 month. These changes observed in the electrocardiograms are believed to have been caused by transient disturbances in the myocardium due to arsenic poisoning.

2. Electroencephalograms

Changes in the central nervous system are sometimes observed in arsenic poisoning. As far as we were able to determine, there are no descriptions in the literature of electroencephalogram findings in arsenic poisoning, and it is even unclear whether there are changes or not. Therefore, electroencephalogram tests were carried out in 11 cases, chiefly hospitalized patients. The ages of these 11 cases were: two less than 3 months, three less than 6 months, four less than 12 months, and two between 1 and 2 years of age. The tests were carried out in mid-September. The test methods were bipolar and unipolar induction. A pen-writing eight-lead Ediswan of British manufacture was used. In some cases soporifics were administered. Of the 11 cases, records for three cases were taken during sleep. The rest of the records were taken during waking. Within the range of our studies, it was not possible to find any particularly noteworthy abnormal findings in the results, and all of the cases remained within the normal range for their ages, chiefly with respect to the delta-theta waves [12]. In other words, it was impossible to find any abnormalities in the electroencephalogram findings in tests conducted about 20 days after discontinuation of ingestion of "MF powdered milk."

3. Concerning Liver Function Tests

We have already reported in our first report [1] that we performed tests of the liver functions by means of the serum cobalt chloride reaction, the cadmium chloride reaction, and the B.S.P. test. As a result, functional abnormalities were observed in many cases. However, with the passage of time, these dysfunctions were recovered. We also reported that there were no symptoms of liver cirrhosis, concerning which there had been concern. Here we report the results of tests performed after the previous report and the subsequent state of recovery of the dysfunctions.

1) Serum cobalt chloride and cadmium chloride reactions. The results are as shown in Table 2. As in the previous report, we followed Iwano [13] in studying the results. The results for 15 cases which had displayed abnormalities in the tests in the past and which had subsequently continued to visit the hospital and for four other cases, altogether 19 cases, were: normal, 15 cases (79.0%); abnormal, 4 cases (21.0%). Among the four abnormal cases, there were three cases with type IIb. The right-hand reaction in the cobalt chloride reactions was quite light, amounting to one or two test tubes. One of these four cases was a hospitalized patient who had displayed considerable changes in the B.S.P. test as well at the time of the previous report. The current state is unclear because the patient ceased to come to the hospital after being discharged because of an accident at the end of December. The other three cases had no other findings at all, and the abnormalities were displayed in this reaction alone.

2) B.S.P. (Bromsulfalein) tests. Tests were made after November of 18 cases who had thus far demonstrated abnormalities as well as six newly added cases, altogether 24 cases. The results obtained are as shown in Table 3. In other words, 23 of the 24 cases (95.8%) displayed normal values, and there were abnormalities in only one case. In late December, this case had a 15% rate of

residue in the blood and was one of the most severe cases who were discharged on account of family circumstances, as described above. In view of the preceding, we can say that in the cases tested by us, no functional disturbances can be observed by the B.S.P. tests today, when half a year has already passed by, except in one case.

Tab. 2
Cobalt and Cadmium Reactions of Serum after 3rd Month

	Number of Cases		
	Out-Pat.	In-Pat.	Total
Type-I	7	8	15
Type-IIa	0	0	0
Type-IIb	3	0	3
Type-IIIa	0	0	0
Type-IIIb	0	0	0
Type-IIIc	0	0	0
Type-IV	0	1	1
Total	10	9	19

Tab. 3
Bromsulfalein Test after 3rd Month

	Number of Cases		
	Out-P.	In-P.	Total
<5%	19	4	23
5~15%	0	0	0
>15%	0	1	1
Total	19	5	24

3) Galactose load tests. In three cases with pronounced liver swelling, galactose loading was performed and the fluctuations of the blood sugar values were tested. No abnormalities were observed except in one case, which had

displayed abnormalities in the B.S.P. tests and in which there was a slight retardation in restoration of the blood sugar values.

4) Concerning liver swelling. Liver swelling was observed in a high percentage of cases (76%) at the beginning. After half a year, the liver swellings have been reduced pronouncedly. That is, there are only six cases in which there are palpable liver swellings of 2 cm or more.

4. Concerning the Adrenal Functions

The adrenal functions were tested in some of the outpatient cases and in all of the hospitalized patients. The testing methods were Thorn's tests and Long's tests. The patients were given either one or both of the tests. Most of the outpatient cases tested were those with medium-degree symptoms.

1) Thorn's tests. The first tests in Table 4 were taken between early and middle September. Only those cases which had abnormal results at this time were given the second tests, which were carried out between middle October and early November.

Tab. 4. Thorn's Test

	First Examination			Second Examination		
	Number of Cases			Number of Cases		
	Out-Pat.	In-Pat.	Total	Out-Pat.	In-Pat.	Total
Normal	7	10	17	7	5	12
Abnormal	9	9	18	1	1	2
Total	16	19	35	8	6	14

First Examination : 4/IX～20/IX
Second Examination : 10/X～10/XI

In the first tests, altogether 35 cases were tested, including 16 outpatients and 19 hospitalized patients. There were 17 normal cases (45.7%) and 18 abnormal cases (54.3%). Thus, abnormalities were observed in approximately half of the patients tested. In the second tests of these cases which had had abnormalities, 12 of the 14 cases were normal (85.7%), and there were only two cases (14.3%) with abnormalities. Thus, the percentage of cases displaying abnormalities had become extremely small. Since early November, the patients have been visiting the hospital about once a month, and the subsequent progress of the two cases with abnormalities is unclear since they have not visited the hospital since then. However, it is supposed on the basis of the above results that the functions improve relatively rapidly.

2) Long's tests. These tests were performed more or less in parallel with Thorn's tests, but there were some cases which were given only one of the tests. The first tests were performed, like the Thorn's tests, from about the beginning of September until the end of September. Testing was performed for a total of 17 cases, including nine outpatient cases and eight hospitalized cases. The results are as shown in Table 5. Abnormal cases were observed at a slightly higher percentage than in the first tests in Table 4. These cases which had displayed abnormalities alone were tested again 1 or 2 months later. The results are summarized as the second test results. Here the ratio between abnormal and normal was the opposite of the results for the first tests. The trend is exactly the same as in the Thorn's tests.

3) Comparison between Thorn's tests and Long's tests. There was an interval of 3-5 days between both tests. The results are shown in Table 6 in comparison with the results for the first tests. Disagreement in the results was seem in six of the 17 cases (35.3%).

Tab. 5. Long's Test

	First Examination			Second Examination		
	Number of Cases			Number of Cases		
	Out-Pat.	In-Pat.	Total	Out-Pat.	In-Pat.	Total
Normal	4	2	6	3	2	5
Abnormal	5	6	11	2	0	2
Total	9	8	17	5	2	7

First Examination : 5/IX～20/IX
Second Examination : 10/X～10XI

Tab. 6.
Thorn's Test and Long's Test

Long's T. / Thorn's T.	Normal	Abnormal	Total
Normal	2 (1)	2 (0)	4 (1)
Abnormal	4 (1)	9 (6)	13 (7)
Total	6 (2)	11 (6)	17 (8)

Numbers in ( ) are In-Patients.

In both tests, there were two cases each which still displayed abnormalities in two or more tests. The subsequent progress of these cases is unknown because they have not visited the hospital.

4) Table 7 was prepared because it was thought that there might possibly be a relationship between arsenmelanosis and the Thorn's tests. Abnormalities in the Thorn's tests are displayed both by those with melanosis and those without melanosis. Therefore, it is not possible to discover any recognizable relationship between both.

5) The results of measurements of the K and Na in the serum and of the 17 ketosteroids in the urine, as well as discussion of these results, are relegated to the biochemical section.

Tab. 7.
Pigmentation and Thorn's Test

Thorn's Test \ Pigmentation	(+)	(−)	Total
Normal	17	0	17
Abnormal	14	4	18
Total	31	4	35

5. Results of Measurements of Arsenic in the Blood

In the previous report [1] we stated our belief that if more than 0.3 γ/cc is found in the blood such results ought to be regarded as abnormal. The results of our measurements after the previous report are shown in Fig. 5. On the basis of these results, it appears possible to presume that a value of more than 0.3 γ/cc is abnormal, as was stated in the previous report. However, the amount of As in the blood will be discussed in detail in the biochemical section.

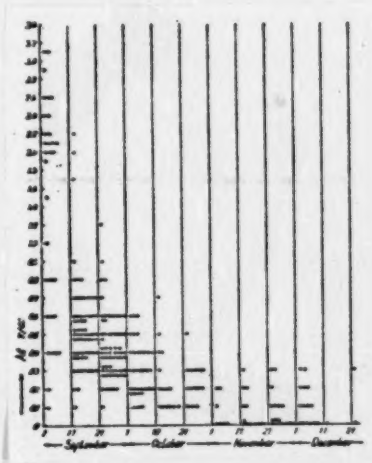

Fig. 5. Amount of As in blood.

6. Bone X-Ray Findings

1) Concerning band-shaped shadows at the long bone ends. In our previous report [1] we stated that rather wide band-shaped shadows were observed in 16 cases (26%) at the long bone epiphysis, although they were not as clear as those observed in lead poisoning. However, we stated that it is not immediately possible to determine whether these changes are caused by arsenic poisoning or not.

Our first tests, covered by our previous report, were carried out last year from the end of August through September. The second tests were performed 3 months later, in later November, and the third tests were performed 6 months later, from the end of February until the beginning of March. Thus, we attempted to discover the progress at 3-month intervals. At this time, we were less interested in determining the positions of the changes; we were more interested in studying the changes undergone by these shadows at the epiphysis with the progress of time, from the first to the second and third tests. For this purpose, we tested 13 cases from the group with band-shaped shadows in the first tests, 12 cases from the group suspected of having them in the first tests, and 10 cases from the normal group. The test results are shown in Table 8, classified according to the findings during the first tests. The findings during the second and third tests were classified into two groups: those in which the findings remained unchanged, and those in which the findings had become less accentuated. As is indicated, the cases which had less accentuated findings in the second and third tests than in the first tests were most numerous in the group with band-shaped shadows, and the ratio between these and the cases with unchanged findings was exactly the opposite of that in the suspected group. The normal group remained entirely unchanged. As for the width of these band-shaped shadows, it was, for example, 2.5-4 mm in the far end of the radius, and the boundaries could be recognized relatively clearly. There

were no cases in which these shadows had become stronger in the second and third tests, but in one case they had become wider by about 1 mm. In the other cases, they either remained unchanged or had become narrower by about 1 mm. As for the manner in which the shadows became less accentuated, in most cases they became less accentuated everywhere, but in some cases the shadows faded out gradually towards the diaphysis so that no clear-cut boundaries could be distinguished. However, it was not possible to observe any pictures of shifts of the band-shaped shadows towards the diaphysis, as are seen in lead poisoning. The appearance of new narrow horizontal lines was observed in five cases. No changes in the shadows of the bone cortex or pictures of periosteum hypertrophy could be observed.

Tab. 8. Follow up X-ray Findings in Epiphyse of Long Bones

First observation / 2nd and 3rd Xray finding / Age (mo.)	Increased density 13Cases				Doubtful 12Cases				Normal 10Cases			
	≦6	≦12	≦24	Total	≦6	≦12	≦24	Total	≦6	≦12	≦24	Total
No change	0	3	1	4	5 (1)	3 (1)	1	9 (2)	3	5 (2)	2	10 (2)
Thinner cases than 1st findings	2	5	2 (1)	9 (1)	0	2	1	3	0	0	0	0

1) Numbers in ( ) are the cases with transverse line
2) No increased original density was seen.

2) Effects of arsenic on long bone growth. In view of the fact that band-shaped shadows were observed in some cases, we attempted to find out what effects are exerted by arsenic on the bone growth, whether directly or indirectly. For this reason, at each X-ray examination measurements were taken of the length of the long bones, in which band-shaped shadows were most frequently observed, chiefly in the ulna (sometimes the radius). To discover whether these bones were developing normally or not, the results were compared with the results of

the roentgenological studies performed by Kitamura [14] concerning the limb bone development of infants in this country. That is, if we calculate the lengthwise growth of the ulna during infancy on the basis of these numerical values, we will obtain a value of 9-16 mm as the normal value for a 6-month period. We regarded a growth of 4-8 mm as retarded growth and a growth of 3 mm or less as pronounced growth retardation. We obtained the following results for 24 cases of infantile arsenic poisoning who were less than 8 months old at the time of the first examination.

Normal growth	10 cases		42%
Retarded growth	11 cases	46%	58%
Pronounced growth retardation	3 cases	12%	

It was observed from the above that bone growth retardation to a greater or lesser degree occurred in the ulna length in about 60% of the cases as a result of arsenic poisoning.

IV. Summary and Discussion

In the foregoing, we have described the clinical findings in infants with arsenic poisoning obtained after the previous report [1] as well as the results of tests which were still incomplete at the time of the previous report. In the following, let us sum up these results and consider them.

1. Those cases which still displayed abnormalities in their electrocardiogram findings in the previous report, after several more tests, had all returned to the normal range by the end of last November, that is, within a period of 3 months. It is supposed from this that the transient abnormal findings such as PQ prolongation, QT prolongation, and drops in T and ST are caused by reversible myocardosis due to arsenic.

2. We tested the liver functions by means of the serum $CoCl_2$ reaction, the $CdCl_2$ reaction, the B.S.P., and in some cases by means of galactose load

testing. In the previous report, there were many cases displaying abnormalities in these testing methods, especially in their serum colloid reactions, and about half of the cases tested had not yet returned to normal. This time, we studied the liver functions in those of the patients with abnormal findings who continued to visit the hospital. Abnormalities were observed in four individual (in three of whom they were extremely slight) in the serum $CoCl_2$ and $CdCl_2$ reactions. In the B.S.P. and galactose loading tests, only one case still displayed abnormalities at the end of last December. This was the most severe case of all the cases tested by us. However, the patient has not visited the hospital since then, and the present state is unknown. As is described above, there have been pronounced improvements in the liver functions, so that there are only a few cases which still have abnormal findings. After half a year has passed by, one must suspend judgment as to whether these abnormalities in the $CoCl_2$ and $CdCl_2$ reactions are still caused by arsenic poisoning alone. At any rate, however, we desire to elucidate this point after continued observations in the future.

3. The adrenal functions were tested by Thorn's tests and Long's tests. In some cases there were still observed findings outside of the normal range, but on the whole there was seen a trend towards improvement, in the same way as in the results of the liver function tests. The other test items, as well as the relationship between the amounts of arsenic ingested and the adrenal functions, are to be considered in the biochemical section.

4. In the previous report, it was stated that arsenic quantities in the blood of more than 0.3 γ/cc are to be considered abnormal. This was established clearly by these studies also.

5. No abnormalities could be observed in the electroencephalogram findings.

6. The patients who in the previous report still retained abnormalities in the three clinical findings of melanosis, white spots and desquamation, and

abnormalities of the nails had returned to normal by about 90% as of the end of last November, that is, after a period of 3 months. The abnormalities disappeared by nearly 100% within 4 months. It was found that recovery in these three symptoms proceeds more or less in parallel and occurs at the same time. The abnormalities in the hair of the head also disappeared in about 4 months.

7. The cases with pigmentation of the gum membranes and the incisors, as well as palpation of the spleen -- these symptoms were described as being doubtful in the previous report -- continued to have them unchanged subsequently, and it becomes more and more doubtful whether these can be ascribed to arsenic.

8. Bone X-rays were taken at 3-month intervals for as many as three times. To summarize the results, the band-shaped shadows at the epiphysis which were seen at the beginning in some of the cases appear to have a tendency to decrease gradually, but it is quite difficult to interpret their meaning. The values obtained by the X-rays were compared with the bone growth values for normal infants given by Kitamura [14]. When the state of bone growth of the arsenic-poisoned infants was measured from the X-ray photographs taken on various occasions, retarded growth of the ulna in the lengthwise direction was discovered in about 60% of the cases. Kitamura's statistics are those made public in 1934, and it is universal knowledge that infant growth at the present time is, generally speaking, much better than it was at that time. If this fact is taken into consideration, one may probably state that there is some impairment of the bone growth of the arsenic-poisoned infants. It would no doubt be suitable to consider both the direct effects and the indirect effects of arsenic on the bone growth.

Next, let us consider in somewhat greater detail the band-shaped shadows at the epiphysis of the long bones which were observed in the first examinations. Similar abnormalities in the X-ray findings for these band-shaped

shadows are found likewise in chronic lead [15], fluorine [16], and phosphorus poisoning [17], in excessive dosages of vitamin D [15, 18], in bismuthosis [19], in Moeller-Barlow disease [20], in congenital syphilis [20], and during convalescence of rickets [20]. We omit detailed considerations concerning the differential diagnosis of these conditions. From the clinical point of view and for other reasons, it is believed possible in this case to exclude the possibility of chronic lead and phosphorus poisoning, bismuthosis, Moeller-Barlow disease, and congenital syphilis. The remaining possibilities are rickets, fluorine poisoning, and excessive dosages of vitamin D. Since the period of occurrence was midsummer, and since there were no other observable findings of rickets, one can hardly assume that these band-shaped shadows are caused by convalescence from rickets. As for fluorine, as was mentioned in the appendix to the previous report, it was found that fluorine also was connected, together with arsenic. That is, it was reportedly determined subsequently that fluorine was present in the powdered milk in the form of $2Na(PAsO_4)$ Na (FOH).22 H_2O. Thus, both arsenic and fluorine ought to have been contained in the powdered milk. Therefore, we estimated the fluorine contents in several samples of the "MF powdered milk" containing the largest amounts of arsenic. We followed the method of Megregian and Meier [21] in quantitative analysis. The results are as shown in Table 9. From these results one may conclude that if lot number MF 5614, which had the highest fluorine contents, were used, even if 100-150 g of powdered milk per day were ingested, the fluorine consumption would be about 550-835 γ/day. Since the daily intake of fluorine was only on this level, and since the period of ingestion was only about 2 or 3 months at the very longest, it would be impossible to assume that band-shaped shadows could occur in the epiphysis as a result of this. Finally, let us consider the possibility of administration of excessive doses of vitamin D. In the 35 cases in which we were able to study the bone X-ray pictures, we investigated whether vitamin D preparations or

comprehensive vitamin preparations had been administered before incidence of this condition. We found that vitamin D preparations had been given in five cases and that the doses amounted to 2-10 drops per day (2000-10,000 international units). Furthermore, all five of these cases were included among the 13 cases in which the band-shaped shadows were observed. In 25 cases (about three-fourths of the cases) comprehensive vitamin preparations had been administered. The quantities used were 0.5-1.0 cc per day (the vitamin D contents would be approximately 200-400 international units). It is also stated that the "MF powdered milk" contained 400 international units of vitamin D in 100 g of the powdered milk. Even if these amounts were added together, the cases given comprehensive vitamin preparations alone would not be receiving excessive doses of vitamin D. In fact, many of these individuals who had been given comprehensive vitamin preparations did not display any abnormalities in the epiphysis at all. From the preceding one may assume that in some of those displaying band-shaped shadows in the epiphysis the administration of excessive doses of vitamin D may have been a cause.

Tab 9
Quantitative Determination of Fluorine

	As	F
MF. 5620	40 γ/g	4.8 γ/g
MF. 5614	44	5.5
Contrast Powder milk	2	1.1
Skim milk	1	0.5

Finally, let us consider the influence of arsenic on the bone tissues. Ōtsuki [22] first of all used young rabbits in experiments concerning the influence of phosphorus on the bone structure. He studied the changes in the bone X-ray pictures caused by phosphorus as well as the bone tissue findings.

He reached the conclusion that these changes in the case of phosphorus are caused by the additive effect during bone formation and by the reduction of the absorption effect. He also [23] administered arsenic to young rabbits for 6 weeks. In the bone X-ray pictures, he observed that arsenic caused changes in the epiphysis, involving the appearance of shadows. He also studied the tissue picture. He held that these bone changes are caused by the reduction of the absorption effect during bone formation, and that reduction of the additive effect is not observed in the case of arsenic. That is, in the tissue findings, the intermediary cartilage layer at the epiphysis is thicker than in the control group, but this is not very pronounced in the reserve calcium layer. However, the primordial medullary cavity is clearly distinguished from the calcified cartilage. They are arranged in a regularly alternating form. Therefore, they form a straight line with respect to the reserve calcium layer. The secondary spongy matter in the young rabbits given arsenic was also far more dense than in the control group, and the medullary cavities were narrower as a result. He holds that these findings are probably explicable by the fact that the absorption of the primary spongy matter has declined in the arsenic-dosed animals. He says that these are the only differences in the microstructure of the spongy matter in comparison with the control groups. Ōtsuki's experiments ended in only 6 weeks. Therefore, in protracted periods of time, as in our observations, it will be necessary to presume the subsequent changes from these tissue findings. That is, if we draw analogy from the tissue findings described above, one would assume that the bone substance would become highly refined, and that with the passage of time horizontal lines would appear and the shadows at the epiphysis would shift towards the diaphysis. Indeed, the appearance of horizontal lines was observed in five cases, but two of these five cases had normal epiphyseal X-ray findings. Thus, it is entirely unclear whether the appearance of these horizontal lines is caused by the direct effect of arsenic or not. Concerning

the appearance of horizontal lines in X-ray pictures for the bones of infants, Okumura [24] states that they appear whenever body weight increase in infants has been stopped or reduced above a certain degree, regardless of what the cause may be. If we accept this theory of Okumura totally, these horizontal lines would be secondary effects caused by the general influence of arsenic on the entire body. It is very possible that this may be true, but there is no reason to deny the direct influence of arsenic. Furthermore, shifts of epiphyseal shadows towards the diaphysis are often observed in lead poisoning, and it is well-known that they are caused by the following. Although there is much deposition of lead in these positions, deposition of calcium is known to play the main role in exerting influence on the X-ray findings. In the arsenic-poisoned infants, we were unable to observe any pictures showing that these band-shaped shadows shifted towards the diaphysis. Since arsenic is far more vulnerable to X-ray absorption than is lead, it is unthinkable that the band-shaped shadows could be caused by the arsenic itself. Even if we were to assume the same mechanism as that occurring during lead poisoning, since the shadows in arsenic poisoning are weak, it is possible that the degree of calcium deposition due to arsenic may be weaker than in the case of lead poisoning. With reference to the appearance of these epiphyseal shadows, as was already mentioned in the previous report, we made a study concerning the amounts of arsenic ingested but were unable to establish any relationship. In the X-ray photographs taken at intervals of 3 months, we also made measurements of some of the long bones and established clearly that there was retardation of the lengthwise growth of the bones. We stated that arsenic influences bone development. However, we do not know whether these effects of arsenic are chiefly direct or indirect, and we merely presume that probably both direct and indirect influences are involved. Concerning the effects of arsenic on the bone changes described above, we will,

in the final analysis, have to await the results of animal experiments. We will report concerning these at some later date.

9. In the previous report, we stated that the arsenic-poisoned infants are making good progress. In this report we may say that this has been confirmed even more. That is, there were some clinical findings in the previous report where the infants still retained abnormalities. In the test results described above, these also have returned to normal with the exception of only a few cases (three or four). Viewed from the body weight increase, the state of growth is also extremely good. In view of these facts, one may say that the subacute and chronic arsenic poisoning by "MF powdered milk" is moving along the path of recovery and has not left in its wake as many abnormalities as were feared at the beginning. With a very few exceptions, almost all cases appear to have been clinically cured. However, may years of continued observation of many patients in the future will be necessary before one can determine what internal changes are present. For example, in connection with the changes in the liver tissues, will there be any reactions towards epidemic hepatitis, ekiri, and other newly contracted diseases? If so, what will be these reactions?

Conclusions

We have described the progress of 134 cases of subacute and chronic arsenic toxicosis in infants caused by "MF powdered milk" for a period of half a year (a period of about 4 months since the previous report), as well as certain clinical test items.

1. In the electrocardiograms, at the time when we compiled our previous report, there were still some cases having abnormal findings (PQ prolongation, QT prolongation), but these cases have all returned to normal within a period of 3 months. Therefore, these changes are presumed to be reversible myocardosis caused by arsenic.

2. In the liver functions, in both of the test methods used by us, the patients recovered with the passage of time and had all returned to normal within 4 months with the exception of three or four cases.

3. The electroencephalogram findings were also studied, but no abnormal findings could be observed.

4. When we were compiling our previous report, three symptoms still remained among the clinical findings. These were: melanosis, white spots and desquamation, and nail abnormalities. These three symptoms recovered in parallel fashion, and abnormalities were no longer observable after 3 to 4 months. The abnormalities in the hair of the head also disappeared in similar fashion. The state of nutrition of the infants is also good.

5. In view of the preceding, as a whole the patients have made good progress (except for one death caused by diphtheric laryngitis not caused by arsenic poisoning). At the present time they are being given health examinations once a month for the sake of precaution, but clinically they may be said to have been almost cured.

6. The shifts in the shadow pictures in the long bone epiphysis, which were observed in some of the cases in the previous report, were followed up by X-ray examinations at 3-month intervals. In some cases there was improvement, and in other cases the abnormalities remained unchanged. The appearance of horizontal lines was observed in five cases. Pictures of shifts of the band-shaped shadows towards the diaphysis were not observed. Various studies were made concerning the possible causes of these findings.

7. 7. Comparative measurements of the lengths of the X-ray pictures for the long bones were made at 3-month intervals. As a result, it was pointed out that some cases displayed retardation of bone growth in the lengthwise direction.

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